Guidelines

Chinese guidelines for diagnosis and treatment of urothelial carcinoma of bladder 2018 (English version)

National Health Commission of the People's Republic of China

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1. Overview

Bladder cancer, which originating from urothelium, is one of the most common malignant tumors in the urinary system. The incidence rate is the eleventh in all malignant tumors worldwide, 9.0/100,000 for men, and 2.2/100,000 for women. The incidence rate is the seventh for men and after tenth for women on malignant tumors; the mortality rate is 3.2/10 million for men and 0.9/10 million for women, and the mortality for men ranks the 9th in male malignant tumors. Regional, racial and gender differences are associated with the pathogenesis of bladder cancer, which are observed in all age groups. The highest incidence is between 50 and 70 years old, which increases with age. Between 2010–2014, the median diagnosis age was 73 years old, and the median age at death was 79 years old based on statistics data from US Surveillance, Epidemiology, and End Results (SEER) database.

The incidence of bladder urothelial carcinoma in China was 6.61/100,000; and the population-standardized incidence was 3.03/ 100,000 according to the statistics of China Cancer Registry Center in 2009. The incidence for men and women is 11.41/100,000 and 3.51/100,000, respectively. The incidence of bladder cancer is 3.3 times for men over the women. The mortality of the disease is 2.60/100,000, 3.75/100,000 for men and 1.24/100,000 for women, respectively. The ratio of patients with urothelial carcinoma of bladder for men and women is about 2.97:1.

In 2016, it is expected to have 80,500 new cases of bladder urothelial carcinoma in China, 62,100 for men (which ranks the 6th in incidence of male malignant tumors in China) and 18,400 for women; there are 32,900 deaths per year for patients with bladder cancer, including 25,100 males (which ranks the 11th in mortality in male malignant tumor in China) and 7,800 female patients.

2. Risk factors for urothelial carcinoma of bladder

Tobacco smoking and long-term exposure to industrial chemical compounds are the external risk factors for bladder cancer. Smoking is the most established and important risk factor for bladder cancer, and it is related to 4-aminobiphenyl, an aromatic amine compound found in tobacco. About 50% of patients have a history of smoking. Smoking can increase the risk of bladder cancer by 2–5 times, and the risk of bladder cancer is also proportional to smoking intensity and length. Stop smoking will gradually lower the risk of bladder cancer.

Urothelial carcinoma of bladder is also associated with chronic inflammation and long-term irritation of foreign objects in bladder (indwelling catheters, stones) and previous exposure to cyclophosphamide chemotherapy. It is also associated with pelvic radiotherapy (RT), abuse of phenacetin and genetic abnormalities.

3. Diagnosis of urothelial carcinoma of bladder

Clinical diagnosis of bladder cancer will be based on patient's medical history, symptoms and signs, and also with laboratory examination, imaging examination, urine cytology, urine tumor marker examination and cystoscopy. Cystoscopy is the most important diagnostic test for bladder cancer. Pathological evaluation with cystoscopy biopsy is the gold standard for the diagnosis of bladder cancer. Imaging studies of the upper urinary tract will determine whether tumor involves each side of renal pelvis or/and ureter.

3.1 Signs and symptoms of urothelial carcinoma of bladder

3.1.1 Symptoms

Hematuria is the most common symptom for bladder cancer. About 80% to 90% of patients have intermittent, whole course-gross painless hematuria as the first sign. The severity, duration and amount of hematuria are not consistent with the degree of malignancy, stage, size, tumor number, and morphology of tumor. Other clinical

manifestations are the irritation symptoms including urinary frequency, urgency and dysuria. These irritation symptoms are common in muscle-invasive bladder cancer (MIBC) or extensive carcinoma *in situ*. Some symptoms happen in late stage of the disease, including lumbar discomfort caused by obstruction of ureter, edema of lower limb, weight loss, renal insufficiency and abdominal or bone pain.

3.1.2 Signs

Patients with bladder cancer generally have no clinical signs. Therefore, physical examination has limited diagnostic value in early stages (such as T1a and Tl). The sign of pelvic mass is associated with locally advanced disease.

3.2 Imaging examination

Imaging examinations include ultrasonography, computed tomography (CT) and CT urography (CTU), magnetic resonance imaging (MRI) and magnetic resonance urography (MRU), intravenous urography (IVU), chest X-ray/thoracic CT, etc. The main goal is to understand the extent of the disease, situation of chest, abdomen, pelvic organs, retroperitoneal and pelvic lymph nodes and upper urinary tract, which will be beneficial for staging the bladder cancer.

3.2.1 Ultrasonography

Ultrasonography is the most widely used and basic examination for the diagnosis of bladder cancer, including abdominal and pelvic ultrasound examinations. The examination can scan kidney, ureter, prostate, pelvic and retroperitoneal lymph nodes and other organs (such as the liver). The image is performed by transabdominal, transrectal/vaginal and transurethral ultrasound. The sensitivity of transabdominal ultrasonography in diagnosis of bladder cancer is 63%–98%, while the specificity is 99%. The kidneys, ureters and other organs in the abdomen can be examined at the same time. Transrectal/vaginal ultrasonography only requires proper urine volume; it could clearly show the triangle, neck of bladder and prostate and tumor base. Transrectal/vaginal ultrasonography is better than transabdominal ultrasound in evaluating the depth of tumor invasion and works well for patients who cannot fill the bladder properly.

Transurethral ultrasonography should be performed under the local anesthesia of the urethra. Although the image may clearly and accurately evaluate the stage of tumor, it is not widely used since it is an invasive procedure.

Color Doppler sonography could scan the signal of the blood flow at the basal part of the tumor, but its value on staging and grading is limited.

The ultrasound manifestation of bladder cancer: the bladder tumor appears as a hypoechoic, patchy or grass watery lesion that protrudes into the bladder cavity. The tumor would not move with the body position; the surface of the bladder wall could be irregular and the wall hierarchy could be disappeared. The ultrasound would find strong or mixed nodule or mass echogenicity with papillary or cauliflower-like, with or without pedicles; tumors may be single or multiple. Color Doppler examination would find the signal of blood flow within or at the edge of the tumor.

3.2.2 CT examination

CT examination (plain scan + enhanced scan): CT scan may diagnose and evaluate the infiltration extent of bladder tumor. It is recommended to evaluate the extent of tumor infiltration if cystoscopy reveals that the tumor has wide base without pedicle, high malignancy and possible muscle-invasive. CT examination may find smaller tumor (1–5 mm), whether it invades lymph nodes or adjacent organs, and distant metastasis, but it does not work well for patients with carcinoma *in situ* and ureter. It can neither accurately distinguish between non-muscle invasive bladder cancer (NMIBC) (Ta, T1) and T2 bladder cancer, nor identify whether the enlarged lymph nodes are metastatic or inflammatory. Studies have shown that the accuracy of CT examination for muscle-invasive cancer is 54.9%, with 39% in low stage, and 6.1% in high stage.

The manifestations of CT scan for bladder cancer could be a local thickening of the bladder wall or a mass protruding into the cavity. The shape of the mass varies and often manifests as papillary, cauliflower and irregular shapes. The outer edge is generally smooth, but it may become rough when the tumor invades beyond the wall. Sandy calcification is common in the inner edge of larger masses, and big and superficial tumors may deform the bladder. Hounsfield unit of plain CT scan on the tumor usually is 30 HU–40 HU, and it demonstrates heterogeneous enhancement with contrast. When the tumor invades beyond the wall, the outline of the bladder is unclear and the fat layer around the bladder obscured. The adjacent tissues and organs may be involved and enlarged pelvic or retroperitoneal lymph nodes may be seen.

CTU: CT/CTU is recommended for patients with multiple, high-risk, and triangle bladder tumors. CTU can provide more information about urinary system (including upper urinary tract, surrounding lymph nodes and adjacent organs), and thus it can replace the traditional IVU.

3.2.3 MRI examination

MRI has superior resolution on soft tissues and is capable of diagnosing and staging the bladder cancer. In patients with T1WI bladder cancer, the signal of urine is very low, low to moderate for bladder wall, and high for fat around the bladder. While for T2WI, the signal for urine is high, low for normal detrusor, and moderate in most bladder tumors. Interruption of low signal in detrusor suggests muscle infiltration.

Dynamic enhanced MRI can show whether there is muscle invasion, the accuracy of which is higher than CT scan or non-enhanced MRI; the accuracy of staging evaluation for T3a tumor is better than that of CT scan, but similar to CT for lymph node evaluation. The staging accuracy of MRI for bladder cancer is 72%–96%, but 32% is over staging. However, the accuracy of whether the tumor infiltrated the muscle layer or confined to the bladder was 85% and 82%. When evaluating bone metastasis, sensitivity of MRI is higher than that of CT, even better than that of radionuclide bone scan.

The apparent diffusion coefficient (ADC) of bladder tumors is lower than that of surrounding tissues, and diffusion-weighted imaging (DWI) is also valuable in assessing tumor invasion of surrounding tissues.

MRU examination: MRU can be used to detect the entire urinary tract, location and cause of upper urinary tract obstruction, and whether there is a tumor in upper urinary tract tumor without contrast agents or not. MRU is especially suitable for patients with contrast allergy, renal insufficiency, failure in IVU and ureterohydronephrosis.

3.2.4 IVU

The aim of IVU examination is to identify whether there is upper urinary tract tumor. Due to low positive rate of IVU examination for diagnosis of upper urinary tract tumors, the risk of misdiagnosis is relatively high, especially when there is no enhancement in IVU due to small tumor in upper urinary tract or hydronephrosis. CTU and MRU are clearer and both have gradually replaced IVU.

3.2.5 Chest plain X-ray film/CT plain scan

Chest plain X-ray examination is a routine test before bladder cancer surgery. It is one of the main screening examinations in case there would be lung metastasis, and it is also a routine examination for postoperative follow-up. Pulmonary metastases may appear as single, multiple or massive diffused round and nodular lesions on chest radiographs. The most sensitive test for pulmonary metastases is chest CT scan. To determine whether there be metastases or not, CT plain scan is recommended for patient with MIBC or for who would receive radical cystectomy.

3.2.6 Bone scintigraphy

Bone scan is not a routine examination but mainly used for patient if there is suspicion of metastases, such as bone pain, elevated serum alkaline phosphatase, or planning for radical cystectomy.

Bone scan is very sensitive and is currently most commonly used for detecting bone metastases in clinical practice. It can discover the bone lesion 3–6 months earlier than the X-ray.

Bone metastatic lesion is characterized by osteolytic change, mostly with abnormal high radioactive concentration, few with radioactive sparseness and defects. The spine is the common metastatic site, followed by the pelvis, ribs, skull, femur and proximal ends of tibia. Bone scan is not specific for bone metastases. CT scan or MRI is used for distinguishing from benignancy and malignancy with single or fewer lesions.

3.2.7 Positron emission tomography-CT (PET-CT)

The tracer fluorodeoxyglucose (FDG) is excreted into the bladder through the kidney, obscuring smaller tumors in the bladder and lymph nodes around the bladder. Together with the high cost, it is not a routine examination. PET-CT is superior to CT and MRI in the diagnosis of lymph node metastasis. It is used in preoperative staging for MIBC, evaluating the metastasis situation and treatment efficacy. PET-CT is not a substitute for MRI and bone scan in the diagnosis of bone metastases due to different imaging mechanisms.

3.3 Urine cytology and tumor marker in urine

Urine-related tests include urinary cytology and tumor markers.

3.3.1 Urine cytology

Detection of cancerous cells in urine is one of the

qualitative diagnoses for renal pelvic cancer, ureteral cancer and bladder cancer. The sensitivity is about 13%–75%, and the specificity is about 85%–100%. The sensitivity is positively correlated with tumor grade. The positive urine cytology of high-grade urothelial carcinoma and carcinoma *in situ* is as high as 84%.

3.3.2 Bladder tumor markers in urine

A variety of urothelial carcinoma screening techniques have been developed, such as nuclear matrix protein 22 (NMP22), bladder tumor antigen (BTA), immunocytochemistry (ImmunoCyt), fibrinogen degradation product FB/FDP, and fluorescence *in situ* hybridization (FISH). Clinical studies have shown a higher sensitivity to detect urothelial carcinoma, but the specificity was still lower than that of urine cytology.

3.4 Cystoscopy and biopsy

3.4.1 Cystoscopy

Cystoscopy and biopsy are the most reliable methods for diagnosing bladder cancer. It is also one of the main measures for monitoring postoperative recurrence of the disease.

Cystoscopy may identify the number, size, shape (papillary or broad-based), location, growth pattern of bladder cancer and any abnormalities of bladder mucosa around the bladder cancer. Biopsy of tumor and suspected lesions may confirm the histological types and grade of cancerous cells.

If carcinoma *in situ* might be suspected in patients with positive urine cytology, a random biopsy should be recommended. But routine randomized or selective biopsy of normal bladder mucosa is not recommended currently for NMIBC due to low probability of carcinoma *in situ* (less than 2%).

3.4.2 Fluorescent cystoscopy

Fluorescent cystoscopy is performed by injecting photosensitizers into the bladder, such as 5-aminolevulinic acid (5-ALA), HAL and pirarubicin. The resulting fluorescent will selectively accumulate in the newly formed bladder mucosa and emit red fluorescence by laser, while normal mucosa appears to be blue fluorescence. Small tumors or carcinomas *in situ* that are difficult to find in common cystoscopy will be identified and the detection rate may increase by 14%–25%.

Fluoroscopy is recommended when bladder cancer *in situ* is suspected or urine cytology is positive while ordinary cystoscopy is normal. The specificity of fluorescent cystoscopy for the diagnosis of bladder cancer was 63%, which was lower than that of normal cystoscopy (81%). The possible causes may be inflammation, recent bladder tumor resection and intravesical therapy for bladder that lead to false positive results.

3.4.3 Narrow band imaging (NBI)

The principle of NBI is to filter out the broadband spectrum including red, blue and green light emitted by ordinary endoscope and retain only narrow spectrum (415 nm and 540 nm). Compared with endoscopy using traditional white light, the microscopic structure of the bladder mucosa and the submucosal blood vessels are more sharpen and the stereoscopic effect is enhanced. It will help early detection and diagnosis of microscopic lesions, improve the detection rate of bladder cancer *in situ* and reduce postoperative recurrence. The sensitivity, specificity and accuracy of NBI cystoscopy are superior to those of ordinary cystoscopy in the diagnosis of bladder carcinoma *in situ* according to the literature. Tumors found only by NBI but not by common cystoscopy accounted for 17.1%. In about 42% of patients with positive urine cytology and negative cystoscopy, bladder tumors were found by NBI cystoscopy.

3.4.4 Diagnostic transurethral resection of bladder tumors (TURBt)

Objectives of diagnostic TURBt are to resect whole tumor, define the pathological diagnosis, grading and staging of the disease, and provide evidences for further treatment and prognosis.

4. Histopathology and staging of urothelial carcinoma of bladder

4.1 Histopathology of urothelial carcinoma of bladder

The current bladder tumor classification guideline adopts "WHO classification of tumors in urinary system and male reproductive organ" with 4th version published in 2016. The tumor classification includes the most common urothelial tumors and some other tumors including squamous cell tumor, glandular tumor, urachal cancer, neuroendocrine tumor, melanoma and mesenchymal tumor. Bladder cancer mainly includes urothelial carcinoma, squamous cell carcinoma (SCC) and adenocarcinoma.

Among them, bladder urothelial carcinoma is the most common one which is accounting for more than 90% of bladder malignancies. SCC accounts for 3%–7% and adenocarcinoma less than 2%. This guideline focuses on the diagnosis and treatment of bladder urothelial carcinoma. The diversification of 2016 and 2004 editions of WHO classification for bladder urothelial carcinoma is listed in *Table 1*, *2*.

4.2 Histological grading, immunohistochemistry and molecular classification of bladder cancer

4.2.1 Histological grading

Grading of bladder cancer is closely correlated with recurrence and invasion behavior. The degree of malignancy is expressed in Grade. The WHO grading standard is currently widely used (WHO 1973, WHO 2004). The 1973 WHO grading standard classifies bladder cancer into highly differentiated, moderately differentiated, and poorly differentiated grades according to the degree of differentiation of cancer cells, which are represented by Grade 1, 2 and 3 or Grade I, II and III, respectively.

The WHO 2004 grading standard classifies urothelial tumors into papillary tumors, papillary urothelial neoplasms of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma and high-grade papillary urothelial carcinoma. The 2004 grading standard is recommended (*Table 3*, 4).

4.2.2 Application of immunohistochemistry detection and molecular classification

In recent years, the International Association of Pathology (ISUP) proposed commonly used markers, among them uroplakin III is the most specific but all have low sensitivity (19%–60%). GATA3 is another commonly used marker, which is expressed in 67%–90% of urothelial carcinomas.

Table 1 WHO 2004 and 2016 versions of non-invasive bladder urothelial tumors

2004 version	2016 version
Carcinoma *in situ* in urinary tract	Carcinoma *in situ* in urinary tract
Low-grade papillary urothelial carcinoma	Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma	High-grade papillary urothelial carcinoma
	Papillary urothelial carcinoma with inverted structure
Papillary urothelial neoplasms of low malignant potential	Papillary urothelial neoplasms of low malignant potential
Urothelial papilloma	Urothelial papilloma
Inverted urothelial papilloma	Urothelial hyperplasia or dysplasia of uncertain malignant potential

Table 2 Comparison of muscle-invasive bladder cancer and its subtypes between WHO 2004 classification system and WHO 2016 classification system

2004 version	2016 version
Invasive urothelial tumors	Invasive urothelial tumors
Infiltrating urothelial carcinoma	Infiltrating urothelial carcinoma with divergent differentiation
with squamous differentiation	Nested, including large nested
with glandular differentiation	Microcystic
with trophoblastic differentiation	Micropapillary
Nested	Lymphoepithelioma-like
Microcystic	Plasmacytoid/signet ring cell/diffuse
Micropapillary	Sarcomatoid
Lymphoepithelioma-like	Giant cell
Lymphoma-like	Poorly differentiated
Plasmacytoid	Lipid rich
Sarcomatoid	Clear cell
Giant cell	Tumors of maullerian type
Undifferentiated	Tumors arising in a bladder diverticulum

Table 3 WHO 1973 and 2004 malignancy grading system for bladder urothelial cancer malignant

WHO 1973 grading system	WHO 2004 grading system
Papilloma	Papilloma
Grade 1: Highly differentiated	Low-grade urothelial papilloma with malignant potential
Grade 2: Moderately-differentiated	Low-grade papillary urothelial carcinoma
Grade 3: Poorly-differentiated	High-grade papillary urothelial carcinoma

Table 4 TNM system of bladder cancer developed by AJCC, 2017

Category	Definition
T—Primary	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ* (flat tumor)
T1	Tumor invades subepithelial connective tissues
T2	Tumor invades muscles
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall and abdominal wall
T4a	Tumor invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N—Regional lymph node	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in a common iliac lymph node(s)
M—Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph nodes metastasis
M1b	Other distant metastases

All the cases express CK7, 67% of the cases express CK20, and 50%–62% of them co-express CK7 and CK20. However, 14% of high-grade urothelial carcinoma expresses CK34Be12 instead of CK7 and CK20. P63 is another highly expressed protein (81%–92%). And S-100P is also a useful marker for urothelial cancer.

Molecular classification of urothelial carcinoma is classified into basal-like (Basal), luminal-like (Luminal) and wild-type P53-like forms according to the expression of CK5/6, CD44, CK20 and P53. It is associated with prognosis and basal-like has the worst prognosis while wild-type P53-like has the best.

4.3 Staging system of urothelial carcinoma of bladder

The most widely adopted TNM classification (2017, 8th edition, *Table 4*) which developed by the American Joint Committee on Cancer Staging (AJCC) is recommended in the present guideline. Based on whether there is invasion of the bladder muscle layer or not, bladder cancer can be classified as NMIBC and MIBC.

5. Treatment principles of urothelial carcinoma of bladder

TURBt is the essential step in the treatment of NMIBC. The protocol of postoperative intravesical therapy is based on the risk of recurrence. Muscle-invasive urothelial carcinoma of bladder, SCC, adenocarcinoma, urachal cancer, etc. require surgery-based comprehensive treatments, and radical cystectomy is the main surgical procedure for these diseases. Some selected patients could be treated with partial cystectomy. Patient with bladder cancer in stage T2−T4a, N0M0 may be treated with neoadjuvant chemotherapy. Systemic chemotherapy and/or RT may be needed after surgery depending on the risk factors from pathological results. Systemic chemotherapy is the main treatment for metastatic bladder cancer. Palliative surgery and RT can be used to relieve symptoms.

6. Treatment of NMIBC (Ta, T1 and Tis)

6.1 Risk grouping system on NMIBC

NMIBC refers to urothelial carcinoma which confined to the bladder mucosa (Tis, Ta) or lamina propria (T1) without any infiltration of muscular layer. NMIBC used to be called superficial bladder cancer. About 75% of patients were diagnosed as NMIBC initially, of which 70% was Ta, 20% was T1, and 10% was Tis. Although Ta and T1 belong to NMIBC, the biological characteristics of the two are significantly different. The T1 disease is easier to metastasize due to abundant vascular and lymphatic vessels in the lamina propria. Risk factors affecting recurrence and progression of NMIBC include number, size, stage, grade, recurrence frequency, and whether it is carcinoma *in situ* or not. The main risk factors associated with recurrence include the number of tumors (≥8) and the frequency of recurrence (>1/year), and the progression is associated with stage (T1), grading (G3 or higher), and whether there is carcinoma *in situ*. NMIBC can be divided into the following three groups according to the risk of recurrence and progression (*Table 5*).

6.2 TURBt and complications

There are two objectives for TURBt, one is to remove all visible tumors, and the other is to remove the tumor tissue for pathological evaluation. The specimen should contain the bladder muscle layer and all visible tumors.

Complete resection of the tumor includes resection in fractions (including tumor, base of bladder wall and margin of the tumor) or *en bloc* resection (it is feasible to use unipolar or bipolar resection, Helium or holmium laser to excise the whole tumor. About 96%−100% of patients have detrusor in the specimen). If the tumor is small (less than 1 cm), then the tumor, the base of the tumor and a partial part of bladder wall should be excised for pathological examination; if the tumor is large, the segment of protruding and base portion of the tumor will be removed until the normal muscle layer is exposed. The muscle layer should be included in the specimen. After all visible tumors have been resected, a piece of basal tissue is cut by an electric loop or a biopsy forceps for pathological examination. These procedures are helpful in determining the pathological stage and treatment protocol. Electrocautery should be avoided to reduce damage to specimen when performing TURBt.

In order to reduce the burden of treatment, recurrent small Ta/G1 tumors found in outpatient cystoscopy may receive directly electrocautery resection. It is one of the alternative treatment methods and no prospective comparative study is available to evaluate the prognosis of the disease.

In a meta-analysis of 12 randomized controlled trials, a total of 2,258 cases of non-invasive bladder cancer with fluorescence cystoscopy guided surgery were compared with conventional surgery. The results show that fluorescence cystoscopy can significantly reduce the recurrence rate, prolong the first recurrence interval and

Table 5 NMIBC risk group system of recurrence

Risk grade	Characteristics
Low-risk of recurrence	Single, initial, low-grade, Ta
Moderate-risk recurrence	Multiple, recurrent low-grade, Ta
High-risk recurrence	Any T1, and/or G3, and/or CIS

NMIBC, non-muscle invasive bladder cancer.

recurrence-free survival time, and increase tumor detection rate. But it failed to significantly reduce the risk of progression to MIBC.

Studies have shown that NBI-guided bladder tumor resection can reduce the 1-year recurrence rate (5.6%) in patients with low-risk NMIBC as compare with white light resection (27.3%). Thus fluorescence-guided or NBI-guided TURBt are preferred according to the researches above.

6.3 Transurethral laser surgery of bladder tumor

Lasers used in clinical applications include 2 μm continuous lasers, holmium, green and thulium lasers. A tumor biopsy is required before surgery to confirm the pathological diagnosis. Laser surgery may coagulate and vaporize tumor, and thus the probability of intraoperative hemorrhage and obturator nerve reflex is low. It is suitable for treatment of non-muscle invasive bladder urothelial carcinoma. The efficacy of transurethral bladder tumor laser surgery is similar to TURBt.

6.4 Photodynamic therapy (PDT)

PDT is a treatment that combines laser and photosensitizer with cystoscope. Singlet oxygen generated by action of laser will degenerate and necrotize tumor cells after the tumor cells taking up the photosensitizer. PDT is suitable for patients with bladder carcinoma *in situ*, repeated recurrence, intolerance of surgery, and failure of BCG intravesical therapy.

Photosensitizers commonly used for intravesical perfusion include 5-aminolevulinic acid (5-HAL) and aminoketovalerate (HAL). The exact curative effect remains to be confirmed by multi-center clinical studies with large sample size.

6.5 Partial cystectomy

Most patients with NMIBC can be excised by TURBt. Isolated solitary tumors with adequate margins and intradiverticular tumors with no carcinoma *in situ* in randomized biopsy are indications of partial cystectomy. Pelvic lymphadenectomy is recommended simultaneously when performing partial cystectomy. It includes lymph nodes from common iliac vessels, internal and external iliac vessels and obturator vessels.

6.6 Radical cystectomy

Radical cystectomy is recommended for NMIBC patients with the following high-risk conditions: multiple and recurrent high-grade tumors, high-grade T1 tumors; high-grade tumors with carcinoma *in situ*, lymphatic vessel infiltration, micropapillary tumors or failure of BCG intravesical therapy. Concurrent chemoradiotherapy or TURBt + BCG intravesical therapy could be applied for patient who does not accept cystectomy. Before making decision, patients should be informed about the advantage and disadvantage of different treatment options.

6.7 Postoperative complications of TURBt

The most common postoperatively complications reported in early stage for TURBt include small amount of hematuria and bladder irritation, which often resolved spontaneously. The main complications include bladder perforation, persistent bleeding and urethral stricture.

6.7.1 Bladder perforation

Intraperitoneal or extraperitoneal perforation should be distinguished. Prolonged indwelling catheter may heal the extraperitoneal perforation. Open surgical repair is recommended for intraperitoneal perforation. The perforation may be prevented by avoiding overfilling the bladder during the TURBt, or applying muscle relaxants to prevent obturator reflex when resecting tumor on each side wall.

6.7.2 Postoperative bleeding

If conservative treatment is not effective for hematuria after TURBt, endoscopic electrocoagulation treatment is the option. In addition to treating wound bleeding, bladder mucosa and neck should be examined and the remaining blood clot be removed. After endoscopic hemostasis, anticoagulant treatment must be temporally stopped and patient should be warned about avoiding raising abdominal pressure.

6.7.3 Urethral stricture

Try to avoid damaging the urethra during TURBt. Urethral dilatation is preferred for mild urethral stricture. The procedure should be gentle to avoid bleeding.

6.8 Secondary TURBt for NMIBC

The significant risk of residual tumor after initial resection

for NMIBC has been demonstrated. Studies have shown that tumor residual after TURBt is associated with stage, size, number and physician's skills. The residual rate for single tumor is 22%, 45% for multiple tumors, 19% if diameter <3 cm, and 42% if diameter >3 cm. For T1 stage with medium- and high-grading bladder cancer, the residual rate was 33%–55% after initial electric resection and 41.4% in TaG3 stage.

Pathological stage deviation may be caused by electrical cutting technique and the quality of the tumor specimens. The likelihood that muscle-invasive disease is detected by re-TURBt of initially T1 tumor ranges from 1.3% to 25% and re-URBT increases to 45% if there was no muscle in the initial resection.

A study of 142 patients treated with TURBt showed that OS is similar if re-TURBt is performed within 2–6 weeks after initial resection, however the rate of recurrence and progression is reduced. In a retrospective multicenter study of 2,451 patients with T1G3/HG, re-TURBt reduced the rate of tumor recurrence and progression in patients without muscle in the specimen from initial resection.

Therefore, a current study has demonstrated that re-TURBt can detect residual tumors, obtain more accurate stage information, increase recurrence-free survival rate, and improve patient prognosis and effectiveness of therapy.

Indications for re-TURBt include: 1) insufficient/incomplete TURBt at previous TURBt; 2) no muscle in the specimen after initial resection, with exception of TaG1 tumors (low grade) and carcinoma *in situ*; 3) T1; and 4) G3 (high grade) with exception for carcinoma *in situ*.

Re-TURBt is recommended about 2–6 weeks after the initial operation. The original tumor site needs to be resected again.

6.9 Postoperative intravesical therapy for TURBt

Intravesical chemotherapy is recommended for all NMIBC patients to prevent planting of tumor cells within 24 h after surgery (immediate intravesical chemotherapy). However, patients with bladder perforation during TURBt or severe hematuria after surgery is prohibited because it may increase the risk of chemotherapeutic agent leakage or bacterial sepsis. Intravesical therapy with BCG is also strictly forbidden in early stage after surgery.

The protocol of intravesical chemotherapy consists of intravesical instillation of chemotherapeutic agent once a week for 4–8 weeks (induction intravesical therapy) in 2–4 weeks after TURBt, and intravesical instillation with the same chemotherapeutic agent once a month for six to twelve months (maintenance intravesical therapy).

Intravesical protocol was formulated based on the recurrence risk grouping: 1) for patients with low-risk NMIBC, immediate intravesical chemotherapy should be performed, but induction and maintenance therapy is not recommended; 2) for patients with intermediate-risk NMIBC, it is generally recommended that all immediate induction and maintenance intravesical therapy be performed, and intravesical therapy with chemotherapeutic agent or BCG in induction and maintenance phase may be optional; and 3) for patients with high-risk NMIBC, after immediate intravesical chemotherapy, induction and maintenance intravesical therapy with BCG is recommended in 2–4 weeks postoperatively.

There is no evidence that different agents show significant differences in the efficacy of intravesical chemotherapy, but intravesical chemotherapy is not recommended for more than one year in general.

Commonly used intravesical chemotherapy agents include pirarubicin (usually 30–50 mg each time), epirubicin (usually 50–80 mg), doxorubicin (usually 30–50 mg each time), hydroxycamptothecin (usually 10–20 mg each time), mitomycin (usually 20–60 mg each time), and gemcitabine (usually 1,000 mg each time). The pH of urine and the concentration of chemotherapeutic agents are related to the effect of intravesical chemotherapy. The water should be banned for 6 h before instillation to reduce the dilution of drug by urine. Drug should be injected into the bladder through the catheter and kept in bladder for 0.5–2 h.

The main side effect of intravesical chemotherapy is chemical cystitis, which is related to the dose and frequency of instillation. The general signs and symptoms of chemical cystitis include frequent urination, urgency and dysuria. In severe cases, it may be accompanied by gross hematuria or urinary bladder mucosa. Mild cystitis can relieve itself during the intermittent period of installation by drinking plenty of water. If severe bladder irritation occurs, intravesical therapy should be delayed or stopped, and most side effects can be relieved after discontinuing of intravesical chemotherapy.

The protocol and dosage of maintenance intravesical therapy with BCG are still inconclusive currently. In patients with high-risk NMIBC, intravesical therapy with BCG is usually performed with 60–120 mg of BCG dissolved in 50–60 mL normal saline, which should retain in bladder for about 2 h each time, and once a week for 6

weeks to induce immune response. In order to maintain and strengthen the efficacy of BCG, installation should be conducted once a week for 3 weeks on month 3, 6, 12, 18, 24 and 36 for 1 to 3 years (at least 1 year). For intermediate-risk NMIBC, 1/3 standard dose is recommended as the effect is the same as the whole dose and the side effects are significantly reduced, however the incidence of severe systemic toxicity is not significantly reduced.

Contraindication: within two weeks after TURBt; severe hematuria; traumatic catheterization; and symptomatic urinary tract infection.

The main side effects of BCG intravesical therapy include bladder irritation, hematuria and systemic flu-like symptoms. Rare severe side effects include tuberculous septicemia, granulomatous prostatitis, epididymal orchitis, joint pain and/or arthritis, allergic reactions, etc.

6.10 Treatment of bladder cancer *in situ*

Although bladder carcinoma *in situ* (Tis) is non-muscle invasive, it is usually poorly differentiated and belongs to highly malignant tumor. Its risk of muscle invasion is higher than that of Ta and T1 bladder cancer. Tis often co-exists with Ta, T1 or MIBC, and is one of the risk factors for poor prognosis.

TURBt alone will not cure Tis. Intravesical therapy with BCG improves the complete remission rate of Tis and reduces the risk of tumor progression compared with intravesical chemotherapy.

The standard treatment for Tis is TURBt, followed by postoperative intravesical therapy with BCG. The complete remission rate for BCG was 72%–93%, which was significantly higher than that of intravesical instillation chemotherapy (48%). It significantly reduced the recurrence and progression rate of the disease. Intravesical chemotherapy can also be selected if the patient is unable to tolerate BCG. About 10%–20% of complete responders treated with intravesical therapy with BCG eventually progress to MIBC, compared with 66% of non-responders

Cystoscopy and urinary cytology are performed every 3–4 months during BCG treatment. Radical cystectomy is recommended if complete remission failed or tumor recurrence or progression occur after 9 months of treatment, or when Tis is associated with MIBC.

6.11 Treatment of recurrent tumor after TURBt

Repeat TURBt is recommended for NMIBC patients if recurrence happened after intravesical chemotherapy. Other chemotherapy drug or BCG can be selected for postoperative intravesical therapy. Preoperative intravesical chemotherapy has no influence on postoperative intravesical therapy with BCG.

Intravesical therapy with BCG or radical cystectomy is recommended for repeated recurrence and multiple lesion patients. Following patients are recommended to perform radical cystectomy: MIBC at follow-up; high-grade NMIBC appeared three months after intravesical therapy with BCG; Tis is found at 3–6 months; and refractory disease with high-grade NMIBC during or after BCG treatment.

6.12 Management for patient with positive urine cytology, negative cystoscopy

If urinary cytology was positive after TURBt re-examination, cystoscopic random biopsy, upper urinary cytology and imaging examination are recommended to determine whether there was a tumor. However, if cystoscopy and imaging examination are negative, then ureteroscope examination is recommended. Intravesical therapy with BCG is recommended if the pathology of the random biopsy confirms Tis. Maintenance intravesical therapy with BCG is needed if there is a complete response. If intravesical therapy with BCG is ineffective or partially relieved, radical cystectomy should be considered, or changing to other installation drugs or drugs from clinical trial. If cytology of urine from upper urinary tract is positive, and the ureteroscopy and imaging examination are positive, the patient should be treated according to the upper urinary tract tumor. Follow-up should be conducted regularly if random biopsy and upper urinary tract examination are negative.

6.13 Follow-up for patients with NMIBC

Ultrasound control is the most routine measure, and cystoscopy is the first-line examination for NMIBC patients. If a suspicious lesion is found in the bladder mucosa during cystoscopy, biopsy should be taken to confirm the pathological results. Urine cytology, CT/CTU or MRI/MRU examinations are performed if necessary; however, cystoscopy can never be fully replaced. All patients with NMIBC are recommended to take their cystoscopy at first three months after surgery, but the cystoscopy can be done in advance if surgical resection is

incomplete and tumor progress rapidly.

Low-risk patients should receive cystoscopy at three months after surgery. If result is negative, second cystoscopy should be repeated once a year and every year for five years. High-risk patients should undergo urine cytology and cystoscopy every three months for the first two years, once every six months from the 3rd year and once a year from the 5th year to lifetime. High-risk patients should take examination for upper urinary tract, such as CTU or IVU, once a year. The follow-up plan for intermediate-risk patients is somewhere in between, depending on prognostic factors and general conditions of individuals. Once a recurrence occurs, the follow-up plan should restart as described above after definitive treatment.

7. Treatment of MIBC

Treatments of patients with MIBC include radical cystectomy, partial cystectomy, neoadjuvant + radical cystectomy/radical cystectomy + adjuvant chemotherapy and bladder preserving comprehensive treatments.

7.1 Radical cystectomy

7.1.1 Indication and contraindication of radical cystectomy

Radical cystectomy with pelvic lymphadenectomy is the standard treatment for MIBC. The indication of radical cystectomy include: 1) T2–T4a, N0–Nx, M0 muscle-invasive BC; 2) Tis with BCG failure, or extensive non-muscle invasive lesions which could not be resected all by TURBt, or high-risk NMIBC with T1G3 (high-grade); 3) BCG refractory bladder cancer; 4) NMIBC with repeated recurrence; and 5) specific histopathological types, such as adenocarcinoma and SCC.

Contraindications of radical cystectomy include: 1) bladder cancer with distant metastasis; 2) severe bleeding tendency; 3) serious complications (heart, lung, liver, brain, kidney and other diseases) and physical weakness whom is unable to tolerate surgery.

7.1.2 Indication of salvage (palliative) cystectomy

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment. It is also used as a purely palliative intervention for patients with fistula formation, pain and recurrent hematuria. Except patients with severe comorbidities (heart, lung, liver, brain, kidney and other diseases) who are unable to tolerate surgery.

7.1.3 Extent of radical cystectomy

The extent of classic radical cystectomy is as follows: bladder and peripheral adipose tissues, distal ureter, and bilateral pelvic lymphadenectomy; in males it should include prostate and seminal vesicles, and in females it should include the uterus, part of the anterior vagina and attachments. Total urethral resection is necessary if tumor invades urethra, bladder neck of female or prostate, or frozen biopsy shows the edge of urethra residual is positive.

For younger male patients who have motivation to preserve sexual function, sexual function-preserving cystectomy (SPC) is the option if tumor is limited or not found in prostate, prostatic urethra and bladder neck. Preserving neurovascular bundle will retain sexual function in some female patients. For patients who choose orthotopic neobladder as urinary diversion, preserving the autonomic nerves which control urethra as much as possible will improve postoperative urinary control. In female patients, vagina could be preserved, and ovary as well for non-menopausal women if tumor does not invade the anterior wall.

The curative effect of cystectomy should not be compromised with the preservation of sexual function, and patients should be closely followed up after operation with preserving procedures. Cystectomy with preserving sexual function is not a standard treatment for MIBC.

7.1.4 Pelvic lymphadenectomy

Pelvic lymphadenectomy is not only a treatment, but also the important information for prognosis. Studies have shown that the risk of lymphatic metastasis in MIBC is more than 24%, and it is also related to the depth of tumor invasion (pT2a: 9%–18%, pT2b: 22%–41%, pT3: 41%–50%, pT4: 41%–63%). Therefore, pelvic lymphadenectomy is an important part of radical cystectomy.

Lymph node dissection includes standard lymph node and extended lymph node dissection. A total of 92% of lymphatic drainage is located below the plane where ureteral across the iliac vessels, therefore standard pelvic lymphadenectomy is recommended for most patients. If the lymph node metastasis is suspected before or during surgery, extended lymph node dissection should be considered.

Standard lymphadenectomy involves removal of nodal tissues cranially up to the common iliac bifurcation with the reproductive femoral nerve being the lateral border, circumflex iliac vein and cloquet lymph node being the distal border, and internal iliac vessel being the rear border

including obturator, internal iliac and extra iliac lymph nodes and sacral lymph nodes.

Extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation, interior of sacral and internal side of iliac vessels at which crossing the ureter, common iliac artery and distal part of abdominal aorta, as well as the area described for standard lymphadenectomy, A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery.

7.1.5 Surgical approaches of radical cystectomy

There are two kinds of radical cystectomy: open and laparoscopic surgery. Laparoscopic surgery includes conventional and robot-assisted laparoscopic surgery.

Laparoscopic surgery requires higher skills for surgeons. Operative time, overall complications, positive rate of postoperative pathological margin and effectiveness of lymph node dissection are similar to open surgery, but it has the advantages of lower blood loss, less secondary damage, mild postoperative pain and quick recovery. Robot-assisted laparoscopic radical cystectomy is more meticulous and conducive to surgeons.

7.1.6 Complications and survival rate of radical cystectomy

Radical cystectomy is a high-risk procedure with perioperative complications about 28%–64% and mortality 2.5%–2.7%. The main causes of death include cardiovascular, sepsis, pulmonary embolism, liver failure and major bleeding. Metastasis of pelvic lymph node is an important factor that significantly affects the prognosis of patients with bladder cancer. A study of 1,054 MIBC patients reported the recurrence-free survival and overall survival were 68% and 66% for 5-year, 60% and 43% for 10 year, respectively. The 5-year recurrence-free survival in pelvic node positive was 34%–43%.

Another study for MIBC patients with radical cystectomy reported the overall 5-year survival was about 54.5%–68%. In a regional lymph node negative patient, the 5- and 10-year survival rates were 89% and 78% for T2 stage, 87% and 76% for T3a stage, 62% and 61% for T3b stage, and 50% and 45% for T4 stage, respectively. In regional node-positive patients, the 5-year survival was only 35%. The 5- and 10-year overall survival rates were from 25% to 35% and 21% to 34% for lymph node-positive patients.

7.2 Partial cystectomy

Partial cystectomy is not the first-line surgical procedure for patients with MIBC. The patient may choose partial cystectomy in the following conditions: a single MIBC (cT2) located at the top of the bladder; the tumor is far from the bladder neck and triangle and it has sufficient surgical margin (no carcinoma *in situ* in other areas of the bladder wall); carcinoma in diverticulum of bladder; and patients are not suitable for total cystectomy with poor physical conditions.

Pelvic lymphadenectomy should be performed simultaneously while performing partial cystectomy. Based on postoperative pathological results (peripheral tissue invasion, metastasis of lymph node, positive margin and pT3–4a) and for patients who do not receive neoadjuvant chemotherapy before surgery, adjuvant RT, chemotherapy or radical cystectomy should be considered.

7.3 Neoadjuvant/adjuvant therapy

7.3.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy combined with radical cystectomy is recommended for patients with cT2–T4a. Adjuvant chemotherapy is recommended for patients with pT3–pT4 or with lymph node metastasis. Without enough convincing evidence, then carboplatin-based chemotherapy could not be recommended for patients who could be tolerate cistoplatin. And immediate radical cystectomy would be recommended for these patients.

Multiple randomized trials and meta-analyses studies have shown that cisplatin-based neoadjuvant chemotherapy can significantly increase the rate of complete tumor response, improve the overall survival and reduce mortality by 10%–13% in MIBC patient. The 5-year overall survival rate increased by 5%–8%, and 11% for cT3 patients. The commonly used neoadjuvant chemotherapy regimens include gemcitabine plus cisplatin: 4 cycles (21 or 28 d for one cycle. 21-d protocol has better compliance); methotrexate, vinblastine, doxorubicin and cisplatin (DD-MVAC) combined with growth factors for 3 to 4 cycles; CMV protocol (cisplatin, methotrexate and vinblastine) for 3 cycles.

For patients with mild renal impairment, Fractional administration of cisplatin-based therapy (eg, 35 mg/m^2 d 1, 2 or d 1, 8) may be considered. Although the program is safer, the relative efficacy is uncertain.

Adverse events and whether they would affect surgery are important factors influencing the decision of neoadjuvant treatment. According to current clinical data, major adverse reactions include digestive tract reaction, anemia and leukopenia. The incidence of grade 3–4

postoperative complications was similar to the group without neoadjuvant chemotherapy. The performance score (PS) >0–1 point, and serum creatinine clearance >50 mL/min are recommended when considering the neoadjuvant chemotherapy.

7.3.2 Neoadjuvant RT for patients with MIBC

Neoadjuvant RT for MIBC with a dose of 45–50 Gy results in pathologically complete response (pCR) about 9%–34%. Some studies suggest neoadjuvant RT can decrease the local recurrence after radical cystectomy. However, limited high-quality evidence supports the use of neoadjuvant RT to decrease the local recurrence of MIBC after radical cystectomy and improve the survival rate. A meta-analysis of five randomized trials showed that there was no significant difference in 5-year survival rates in MIBC patients with neoadjuvant RT, therefore, neoadjuvant RT is not recommended currently.

7.3.3 Adjuvant chemotherapy for patients with MIBC

There is neither prospective evidence nor conclusive results on whether adjuvant chemotherapy should be performed after cystectomy in patients with MIBC. A number of meta-analysis studies showed that adjuvant chemotherapy reduced the risk of death by 23% and improved recurrence-free survival in MIBC patients after radical cystotomy. A retrospective study of 5,653 patients undergoing radical cystectomy had 23% of them treated with adjuvant chemotherapy, and the result of the study seemed that adjuvant chemotherapy could improve overall survival of patients.

Evidence-based studies showed that the improvement for survival of non-metastatic MIBC treated with adjuvant chemotherapy was not as effective as neoadjuvant chemotherapy. Some clinical studies confirm that adjuvant cisplatin-based combination chemotherapy can reduce tumor recurrence rate in high-risk recurrence patients, which was benefit for MIBC (pT3/4 and/or pN + M0), especially for patients who did not receive neoadjuvant chemotherapy. Currently, platinum-based combination chemotherapy is commonly used in clinical practice.

7.4 Comprehensive treatment for preservation of bladder for patients with MIBC

Comprehensive treatment of preserving bladder may be an option for MIBC patients who are unwilling or unable to undergo radical cystectomy. However, some controversies still exist which need to be carefully considered.

There are two surgical approaches for preserving the bladder: TURBt and partial cystectomy. For most MIBC patients, the fundamental procedure to preserve bladder is to remove the tumor thoroughly with TURBt and adjuvant RT, however the risk of lymph node metastasis is relatively high in patient with MIBC. Discussion with patients who choose to preserve bladder and making a decision together should be very important, which includes comprehensive evaluation of the nature of the tumor, the depth of invasion, surgical procedure to preserve the bladder, adjuvant chemotherapy and RT, close follow-up and salvage cystectomy if necessary. The 5-year overall survival rate for patients with MIBC who underwent comprehensive treatment for preserving bladder ranged from 45% to 73%, and the 10-year from 29% to 49%.

There are several bladder preserving strategies currently: 1) TURBt alone: if tumor is limited to the superficial muscle layer and re-TURBt is negative, patients usually receive intravesical therapy with BCG after surgery; 2) TURBt combined with external radiation therapy: mainly for patients who are not suitable for radical cystectomy or could not tolerate chemotherapy. The 5-year survival rate is 30%–60%, and the tumor-specific survival is 20%–50%; 3) TURBt combined with chemotherapy: the complete response rate is 8%–26%. Cisplatin-based chemotherapy is used in T3/4 patients, complete response and partial response rates are 11% and 34%, respectively. Patients should perform salvage radical cystectomy after 3 cycles of chemotherapy if re-staging of biopsies is positive with cystoscopy; 4) TURBt combined with RT and chemotherapy: cisplatin-based chemotherapy combined with RT can achieve a complete response rate of 60%–80% after maximal TURBt. The 4–5-year survival rate is about 40%–45% for MIBC patient with bladder preservation, and long-term survival is 50%–60% (similar to radical cystectomy). However early radical cystectomy is recommended if patients are not sensitive to comprehensive treatment; and 5) partial cystectomy combined with chemotherapy: only about 5% of MIBC can be cured by partial resection, and about 27% of patients may avoid radical cystectomy.

Preserving bladder through single treatment is difficult to achieve. Current treatment will include combination of surgery, chemotherapy and RT. The indication must be strictly controlled, and the patient must have good compliance in order to get better prognosis.

The basic treatments for cT4b patients with negative lymph node are systemic chemotherapy or RT combined

with chemotherapy. The efficacy was assessed after 2–3 cycles of chemotherapy, or 3 cycles of RT at dose 40–45 Gy. If residual biopsy is positive or progressed after comprehensive treatments, palliative cystectomy could be considered, another option is the second-line chemotherapy regimen.

For cT4b patients with positive lymph node, systemic chemotherapy or concurrent chemoradiotherapy is recommended. Increasing RT dose or palliative cystectomy could be considered if tumor is still progressing. Palliative cystectomy with urinary diversion would be considered if there is severe hematuria and hydronephrosis.

7.5 External beam radiotherapy (EBRT)

EBRT is the option for MIBC patients who are intolerant of radical cystectomy or do not accept it. It can only be chosen as one of comprehensive treatments aimed at preserving the bladder.

A study of 340 patients with MIBC was divided into EBRT alone, EBRT + chemotherapy, or neoadjuvant chemotherapy + EBRT. The overall complete response rate was 55%, and the 10-year disease-specific survival and overall survival were 35% and 19%, respectively. The complete response rate was 64% for EBRT alone, 79% for EBRT + chemotherapy, and 52% for neoadjuvant chemotherapy. The absence of Tis, the younger age and the lower tumor stage are associated with better survival.

7.6 Urinary diversion

There is no standard protocol for urinary diversion, and several types of urinary diversion can be chosen including uncontrolled urinary diversion, controlled urinary diversion and intestinal neobladder.

7.6.1 Orthotopic neobladder

A successful orthotopic neobladder should meet the following conditions: 1) intact urethra and sufficient external sphincter function; 2) intraoperative negative urethral margins; 3) good renal function; and 4) no obvious intestine lesion.

Disadvantages of orthotopic neobladder include urinary incontinence and dysuria, and possible long-term catheterization or self-guided intermittent catheterization.

Contraindications: high-dose preoperative RT, complicated urethral stricture, disabled patients, and tumor invasion to bladder neck and urethra.

7.6.2 Ileal conduit

Urinary diversion with ileal conduit is a classic, simple, safe and effective uncontrollable urinary diversion procedure. It is the most commonly used procedure for urinary diversion. The main disadvantage is the need of abdominal wall stoma and wearing a urine collection bag lifetime.

If ileum cannot be used, colon conduit may serve as an alternative procedure. Transverse colonic conduit should be considered for patients who have undergone pelvic RT or patients whose ureter is too short.

7.6.3 Cutaneous ureterostomy

Cutaneous ureterostomy is a simple, safe procedure for patients with short expected survival time, or with distant metastasis, or without proper intestine for urinary diversion, and all patients who have poor general condition. The risk of stoma stenosis and retrograde urinary tract infection of cutaneous ureterostomy is higher than ileal conduit.

7.6.4 Other methods of urinary diversion

Other urinary diversions include percutaneous urinary controlled pouch and anus urinary diversion. All those above are not widely applied in clinic practice currently.

8. Treatment of metastatic urothelial carcinoma of bladder

The main treatment approaches for metastatic urothelial carcinoma of bladder include systemic chemotherapy, chemotherapy combined with RT or RT alone.

Cisplatin-based combination chemotherapy is the most important chemotherapy regimen for metastatic urothelial carcinoma of bladder.

Urothelial cancerous cells are proved to be sensitive to chemotherapeutic agents such as platinum, gemcitabine, doxorubicin and paclitaxel. The common first-line chemotherapy protocols include GC, DD-MVAC (modified MVAC enhancement regimen), MVAC, etc. The overall response rate can reach 50% for patient with metastatic disease while treated with platinum-containing combined chemotherapy. Almost all patients with metastatic bladder cancer would progress when being treated with systemic chemotherapy and they had only 14 months in median progression-free survival, only about 5%–20% with 5-year cancer-specific survival rate.

8.1 Surgery for patients with oligometastatic bladder urothelial carcinoma

Multiple retrospective studies have confirmed that resection of oligometastasis in patients with metastatic bladder urothelial carcinoma is beneficial to prolong survival, especially in patients with good response to chemotherapy, isolated metastases, lung metastases or positive lymph node. A meta-analysis of 412 oligometastase bladder cancer patients indicates that oligometastasis resection can improve the overall survival as compared with non-operative group, and the 5-year survival rate can reach 28%–72%. Currently, due to limited relevant information, surgery for oligometastasis is an option only for few selected patients with metastatic bladder cancer.

8.2 Systemic chemotherapy

8.2.1 First-line systemic chemotherapy for metastatic bladder urothelial carcinoma

For patients who can tolerate cisplatin: gemcitabine plus cisplatin; DD-MVAC combined with granulocyte colony-stimulating factor (G-CSF).

For patients who cannot tolerate cisplatin: carboplatin plus gemcitabine; Atezolizumab and Pembrolizumab; gemcitabine combined with paclitaxel; or ifosfamide, doxorubicin, gemcitabine monotherapy (if patients have good kidney function and physical condition).

(1) GC regimen (gemcitabine combined with cisplatin)

The GC regimen is currently the most commonly used first-line chemotherapy regimen in clinical practice. The adverse events are lower than that of MVAC regimen, but efficacy is the same. In one cycle, the protocol consists of intravenous infusion of 1,000 mg gemcitabine on d 1 and d 8, 70 mg of cisplatin on d 2 for three weeks (21 d program). In metastatic bladder cancer patients treated with GC regimen, complete response rate is 15%, partial response rate is 33%, a median disease progression survival is 23 weeks, and overall survival is only 13.8 months.

(2) Modified MVAC enhancement regimen

DD-MVAC regimen consists of intravenous administration of 30 mg/m^2 methotrexate on d 1, 3 mg/m^2 of vinblastine, 30 mg/m^2 of doxorubicin, 70 mg/m^2 of cisplatin on d 2 every 2 weeks. Granulocyte colony-stimulating factor is routine used for prophylactic purpose in period of chemotherapy. Since the side effects are low and the efficacy is similar to that of MVAC regimen, it has gradually replaced the MVAC regimen.

(3) CMV regimen

Intravenous administration of 30 mg/m^2 methotrexate, 4 mg/m^2 vinblastine on d 1 and 8, 100 mg/m^2 cisplatin on d 2 every 3 weeks for one cycle. Generally, three cycles are applied. In a phase III clinical trial, CMV regimen has been shown to reduce mortality by 16% and increase the 10-year survival by 6%. The regimen can be applied as neoadjuvant chemotherapy.

Chemotherapeutic agents in second-line treatment include: docetaxel, paclitaxel, gemcitabine, pemetrexed, ifosfamide, doxorubicin, etc. Single or combined chemotherapeutic agents could be selected depending on the patient's tolerance, and zoledronic acid is the option for the treatment of bone metastases.

8.3 Immunotherapy for metastatic bladder urothelial carcinoma

Currently, PD-1/PD-L1 immune checkpoint inhibitors are main imunnotherapy medicines, which include Atezolizumab, Durvalumab, Avelumab, Pembrolizumab and Nivolumab. These immune checkpoint inhibitors can serve as second-line treatment when patients with metastatic disease are failed with platinum-based chemotherapy. Atezolizumab and Pembrolizumab can also be used as first-line treatment for those who could not tolerate platinum-based chemotherapy.

9. RT for bladder cancer

RT or combined with chemotherapy would be options for patients with muscle-invasive disease when those patients are unwilling to undergo radical cystectomy, or they could not tolerate radical cystectomy because of poor general condition. It is also an option for patients with unresectable disease.

However, RT alone has shorter survival time than those treated with radical cystectomy in MIBC patient. RT is divided into radical RT, adjuvant RT and palliative RT. The 5-year overall survival, cancer-specific survival and local recurrence rate of radical RT are 40%–60%, 35%–40%, and 30%, respectively. Residual tumor after radical cystectomy may also be treated with adjuvant RT. Palliative RT for extremely advanced disease with cT4 may effectively relieve symptoms such as bleeding and pain, and improve the patient's quality of life.

10. Comprehensive treatment for patients with uncurable bladder cancer

10.1 Palliative cystectomy

Patients with locally advanced urothelial carcinoma of bladder (cT4) may choose palliative cystectomy and cutaneous ureterostomy or permanent nephrostomy to relieve upper tract obstruction, bleeding, pain and dysuria. All those approaches above may improve renal function providing chance of safer chemotherapy in the future.

10.2 Symptomatic treatment

Patients with incurable bladder cancer usually have the following symptoms: pain, bleeding, difficulty urinating and upper urinary tract obstruction. Supportive care has important implications for these advanced-stage patients.

10.2.1 Bleeding and pain of bladder

Coagulation disorders or anticoagulant agents history must be screened if severe hematuria occurs in patient with incurable bladder cancer. Transurethral electrocoagulation or laser coagulation may be difficult to apply in a bladder with full of tumor. Intravesical instillation with 1% silver nitrate or 1%–2% alum could be effective and can usually be done without any anesthesia. RT is also used to control bleeding and pain. If all approaches above cannot control bleeding, urinary diversion with or without palliative cystectomy would be the last choice.

10.2.2 Upper urinary tract obstruction

Ureteral stent (preferred), nephrostomy provide an effective solution for upper urinary tract obstruction for patients with advanced-stage bladder cancer. If Double-J stent is difficult to implant into the renal pelvis and patient refuses bilateral nephrostomy, urinary diversion is also another possible solution to relieve upper urinary tract obstruction, with or without a palliative cystectomy.

11. Follow-up for MIBC

Long-term follow-up is necessary for patients with urothelial carcinoma of bladder when they undergo radical cystectomy and urinary diversion. Tumor recurrence and complications associated with urinary diversion are the fucus.

12. Non-urothelial carcinoma of bladder

12.1 SCC of bladder

Bladder SCC is divided into non-schistosomiasis and schistosomiasis bladder SCC, and the former is more common in China.

Chronic inflammation caused by bacterial infection, foreign body, chronic lower urinary tract obstruction or bladder stones, as well as leukoplakia of bladder mucosa and long-term indwelling catheter may be related to the occurrence of bladder SCC.

Bladder SCC usually happens in trigone and lateral wall of the bladder as ulcers and infiltration, rarely papillary-like lesion. About 8% of bladder SCC has metastasis at the time of diagnosis.

Hematuria is the major symptom with 93% of patients experience urinary tract infection. Cystoscopy biopsy is the main diagnostic examination.

Radical cystectomy is recommended for patients with simple bladder SCC. It is superior to RT although some patients choose partial cystectomy. Preoperative RT plus radical cystectomy has better efficacy than radical cystectomy alone in preventing pelvic recurrence. RT alone is not effective and thus it is not recommended. The efficiency of chemotherapy for bladder SCC is very low due to lack of effective chemotherapy regimen. The 5-year survival rate of bladder SCC is approximately 50%.

12.2 Adenocarcinoma of bladder

Bladder adenocarcinoma is divided into three types according to tissue source: primary non-urachus adenocarcinoma, urachal adenocarcinoma and metastatic adenocarcinoma. Cystoscopy biopsy, ultrasound, CT and MRI will provide information about tumor size, extent of invasion and clinical stage, especially for urachal adenocarcinoma.

12.2.1 Primary non-urachus adenocarcinoma of bladder

Non-urachus adenocarcinoma of bladder is associated with adenoid metaplasia. Long-term chronic irritation, obstruction and bladder extrophy are common causes of metaplasia and often accompanied with cystitis glandularis.

Hematuria, dysuria, bladder irritation and mucous discharge are most common clinical signs of adenocarcinoma. Primary bladder adenocarcinoma is mostly invasive bladder cancer. It occurs in the triangle area and the lateral wall of the bladder and develops rapidly. Most

tumors are in advanced stage in clinical visit and radical cystectomy is usually recommended. Transurethral resection or partial cystectomy is less effective. Postoperative RT will improve the recurrence-free survival rate. Patients with advanced and distant metastases diseases can choose chemotherapy, and a 5-fluorouracil-based chemotherapy regimen is recommended.

12.2.2 Urachal adenocarcinoma

Urachal adenocarcinoma accounts for about 1/3 of bladder adenocarcinoma and is usually associated with urachal epithelial hyperplasia and its intrinsic transitional epithelial gland metaplasia. Urachal adenocarcinoma occurs in the anterior wall of the bladder and can infiltrate into the deep layers of the bladder wall, the umbilicus, the Retzius gap and the anterior abdominal wall. The stage of urachal adenocarcinoma is usually high when diagnosed and so is the chance of distant metastasis.

Treatment of urachal adenocarcinoma: surgery is the most important therapy which includes extended partial cystectomy and radical cystectomy. The effects of RT and chemotherapy are poor.

Extended partial cystectomy: including removing the entire section of the bladder top, umbilical ligament and umbilicus. The range of resection includes partial rectus abdominis muscle, posterior rectus sheath, peritoneum and arcuate line. Postoperative recurrence and metastasis are main indications of treatment failure. Negative surgical margins and lymph node are important factors affecting the prognosis. The overall 5-year survival rate is 40%, and the average survival time is 46 months.

12.3 Small cell carcinoma of bladder

Histologically similar to small cell carcinoma of lung, bladder small cell carcinoma occurs mostly on both sides and at the bottom of the bladder. The size of tumor is usually large with average size about 5 cm. The tumor is usually invasive and distant metastases are common. Patients with small cell carcinoma often have deep muscle infiltration at initial diagnosis. The diagnostic examinations include cystoscopy and biopsy. Imaging examination could define the range of invasion and whether there is any distant metastasis.

Treatment will generally be combination of chemotherapy and topical therapy. Adjuvant chemotherapy or neoadjuvant chemotherapy should be recommended. Topical treatment usually includes surgery or RT. Studies suggested that neoadjuvant chemotherapy would improve the survival of patients with the disease. Radical cystectomy is selected as a proper surgical treatment. Adjuvant chemotherapy should be considered for patients with T3 and T4 disease. The chemotherapy regimen of cisplatin combined with etoposide is generally used.

13. Quality of life of patients with bladder cancer

Health-related quality of life (HRQoL) research has been widely adopted in the screening of treatment methods for cancer and evaluation of therapeutic effects, etc.

The assessment of HRQoL for patients with bladder cancer includes physical, emotional and social activities as well as related complications (such as urination problems, urinary fistula, skin problems and sexual function problems). Forms of FACT, EORTC QLQ-C30, FACT-BL and FACT-VCI are designed and validated for patients. Urologists should pay full attention to HRQoL, and discuss the treatment options and complications with patients in order to get better quality of life for patients.

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